Claims

1. A process for generating a combinatorial set of molecules of core structure M, comprising the steps of:

(a) preparing a plurality of immobilized molecules of core structure M, wherein said molecules contain a plurality of reactive moieties, each reactive moiety being blocked by a blocking group, wherein at least three of the blocking groups are independently removable under at least three different conditions; and

(b) removing certain blocking groups and derivatizing the resulting reactive moieties in a preprogrammed, regioselective manner, wherein each member of a combinatorial set is uniquely derivatized at at least one reactive moiety with a unique substituent, thereby generating a combinatorial set of molecules of core structure M.

2. A process for generating a combinatorial set of oligomers, comprising the steps of:

(a) preparing a plurality of immobilized molecules of core structure M and containing a plurality of reactive moieties, each reactive moiety being blocked by a blocking group, wherein at least three of the blocking groups are independently removable under at least three different conditions; and

(b) removing certain blocking groups and derivatizing the resulting reactive moieties in a preprogrammed, regioselective manner, wherein at least one reactive moiety is derivatized by addition of a preselected monomer, and said monomer contains a plurality of reactive moieties, each reactive moiety being blocked by a blocking group, wherein at least one of the blocking groups can be independently removed under at least one of the three different conditions;

(c) sequentially performing step (b) for the appropriate number of cycles to obtain an oligomer comprising the desired number of monomers, wherein each member of a combinatorial set is uniquely derivatized at at least one reactive moiety with a unique substituent, thereby generating a combinatorial set of oligomers, which are comprised of the same number of monomers, but which differ in the composition of at least one monomer or in the derivatization of at least one reactive moiety within at least one monomer.

3. A process of claim 1, wherein the immobilized molecule is a multifunctional, low molecular weight compound of the general formula MD_n, wherein D represents the same or different independently deprotectable moieties and n is an integer from 3 to 10.

4. A process of claim 3, wherein the low molecular weight compound is selected from the group consisting of a: saccharide, aminosugar, deoxysugar, nucleoside, nucleotide, coenzyme, amino acid, lipid, steroid, vitamin, hormone, alkaloid and small molecule drug compound.

5. A process of claim 2, wherein step (b) is performed for the appropriate number of cycles to obtain an oligomer comprised of a number of monomers in the range of about 2 to about 100.

6. A process of claim 2, wherein the oligomeric compound is selected from the group consisting of: an oligosaccharide, oligopeptide and oligonucleotide.

7. A process of claim 6, wherein the oligonucleotide is derived from a 2'-deoxyribonucleoside and/or a ribonucleoside.

8. A process of claim 7, wherein the oligonucleotide is synthesized in the 3' to 5' or 5' to 3' direction.

9. A process of claim 8, wherein the oligonucleotide is synthesized according to the phosphoamidite, H-phosphonate, or phosphotriester method.

10. A process of claim 6, wherein the oligonucleotide contains a natural or modified base selected from the groups consisting of: adenine, guanine, cytosine, uracil, 5-fluoro-uracil, 5-chloro-uracil, 5-bromo-uracil, 5-iodo-uracil, 5-fluoromethyl-uracil, 5-chloromethyl-uracil, 5-bromomethyl-uracil, 5-iodomethyl-uracil, 5-aminomethyl-uracil, 5-hydroxymethyl-uracil, 5-mercaptomethyl-uracil, 5-fluoro-cytosine, 5-chloro-cytosine, 5-bromo-cytosine, 5-iodo-cytosine, 5-azido-cytosine, 5-alkyl-cytosine, 5-ω-aminoalkyl-cytosine, 5-azido-uracil, 5-alkyl-uracil, 5-ω-aminoalkyl-uracil, 5-methyl-cytosine, 5-amino-cytosine, 5-amino-uracil, 4-triazolo-uracil, 4-triazolo-thymine, 4-tetrazolo-uracil, 4-tetrazolo-thymine, hypoxanthine, xanthine, 2,6-diamino-purine, 6-chloro-purine, 2,6-dichloropurine, 6-thio-purine, 2-thio-purine, 8-fluoro-adenine, 8-chloro-adenine, 8-bromo-adenine, 8-iodo-adenine, 8-fluoro-guanine, 8-chloro-guanine, 8-bromo-guanine, 8-iodo-guanine, 8-amino-adenine, 8-amino-guanine, 8-hydroxy-adenine, 8-hydroxy-guanine, 8-thio-adenine, 8-thio-guanine, N7-deaza-adenine, N7-deaza-guanine, N3-deaza-adenine, N3-deaza-guanine, N9-deaza-adenine, N9-deaza-guanine.

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11. A process of claim 1 or 2, wherein the reactive moieties are selected from the group consisting of: OH, SH, NH_2, CO_2H, SOH, SO_2H, SO_3H, CHO, keto, phosphate, phosphite, phosphoamidite, halogen, CN, CNS, NCS, NCO and derivatives thereof.

12. A process of claim 1 or 2, wherein the molecule has been immobilized based on linkage to a solid support.

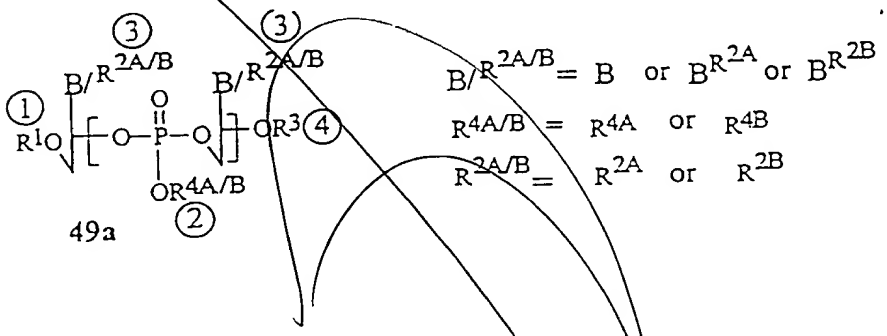
13. A process of claim 12, wherein the solid support is selected from the group consisting of: beads, flat supports, wafers with or without pits and/or channels, the bottom of a microtiter plate or the inner walls of a capillary.

14. A process of claim 13, wherein the beads are comprised of a material selected from the group consisting of: polystyrene, polyamide, cellulose, Sephadex, Sepharose, silica gel, controlled pore glass (CPG), and teflon.

15. A process of claim 12, wherein the linkage can be cleaved under acidic, alkaline, neutral or photolytic conditions.

16. A process of claim 15, wherein the linkage is selected from the group consisting of tritylether, ester, ß-benzoylpropionyl, levulinyl, disulfide, sulfenyl and derivatives thereof.

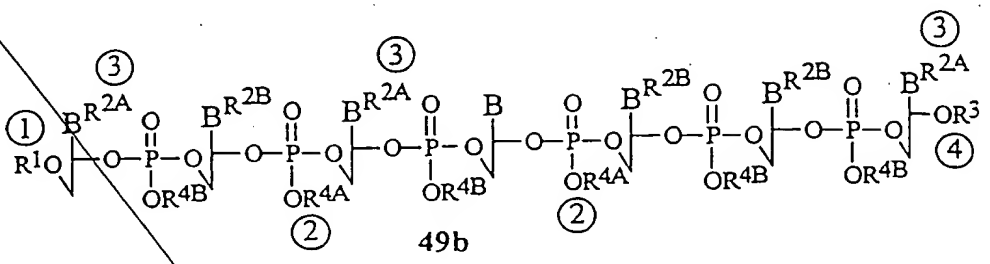
17. A composition comprising an oligonucleotide, which is further comprised of monomers of the general formula **49a**:



49a

in which ①, ②, ③, ④ are positions in the molecule which can be addressed regioselectively and in which B represents a natural or modified nucleobase, which does not require a protecting group during synthesis, B^{R2A}, B^{R2B} is a natural or modified nucleobase with a protecting group and R^{2A}, R^{4A}, R^1, and R^3 represent different protecting groups that permit the creation of a combinatorial set of oligonucleotides with 16 possible states of protection or subsequent derivatization at positions ① - ④ and R^{2B}, R^{4B} represent protecting groups which are stable during deprotection and/ or subsequent derivatization at ① - ④.

18. A composition of claim 17, which is of the formula:

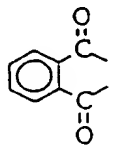


49b

19. A composition of claim 17, wherein the oligonucleotide is deprotected or derivatized in 64 different regioselective combinations, by using 2-nitrophenylsulfenyl as R^{2A} for the protection of adenine (A), cytosine (C) or guanine (G).

20. A composition of claim 17 or 18 in which R^{2A} or R^{2B} is a base protection group selected from the group consisting of an acyl group, which is selected from the group consisting of: acetyl, benzoyl, anisoyl, p-/o-tolyl, phenoxyacetyl, t-butylphenoxyacetyl or 2-nitrophenylsulfenyl (nps), 2-(4-nitrophenyl)-ethoxycarbonyl (npeoc), 2-(4-nitrophenyl)-ethyl (npe), 9-fluorenylmethoxycarbonyl (Fmoc), benzyloxycarbonyl, benzyl, allyloxycarbonyl, N,N-dimethylaminomethylidene (DMM) and derivatives thereof, p-nitrobenzylidene, levulinyl, compound **50** or a derivative thereof, compound **51**, trityl, monomethoxytrityl, dimethoxytrityl, trimethoxytrityl, 2,2,2-trichloro-*tert*-butyloxycarbonyl (TCBOC), R^{4A} or R^{4B} is a phosphate protecting group selected from the group consisting of an alkyl, aralkyl, allyl, ß-cyanoethyl, o-/-p-chlorophenyl, 2,5-dichlorophenyl, trichloroethyl, tribromoethyl, sulfonylethyl or derivatives thereof, 4-*tert*-butyl-2-chloro-phenyl, phenylmethylamino, 2,4-dichlorophenyl, m-chlorophenyl, o-fluorophenyl, benzyl, benzhydryl, ß,ß,ß-trichloroethyl, 4-nitro-2-chloromethyl-phenyl, 2-(4-nitrophenyl)-ethyl (npe), 4-nitrophenyl, compound **52** and **53**, R^3 is the 3'-OH functionality, selected from the group consisting of trityl, substituted trityl, triphenylmethoxyacetyl, diphenyl-*tert*-butylsilyl, succinyl, ß-benzoylpropionyl, levulinyl, *tert*-butyl-dimethyl-silyl, 2,4-dinitrophenylsulfenyl (dnps), 9-fluorenylmethoxycarbonyl (Fmoc), 3-{4-[bis-(4-methoxyphenyl)-methyl]-phenyl}-propionyl, 5-{3-[bis-(4-methoxyphenyl)-hydroxymethyl]-phenoxy}-levulinyl, 5-{3-[bis-(4-methoxyphenyl)-methoxymethyl]-

phenoxy}-levulinyl or the linkage to a solid support and $\mathbf{R^1}$ is the 5'-OH functionality selected from the same group as for $\mathbf{R^3}$.



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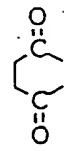

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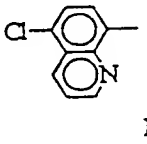

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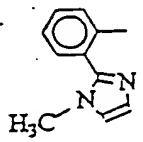

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21. A composition of claim 17, wherein $\mathbf{R^{2A}}$ is 2-nitrophenylsulfenyl (nps), $\mathbf{R^{2B}}$ is 2-(4-nitrophenyl)-ethoxycarbonyl (npeoc) and 2-(4-nitrophenyl)-ethyl (npe) or npeoc, $\mathbf{R^3}$ is 5-{3-[bis-(4-methoxyphenyl)-hydroxymethyl]-phenoxy}-levulinyl or 5-{3-[bis-(4-methoxyphenyl)-methoxymethyl]-phenoxy}-levulinyl, $\mathbf{R^{4A}}$ is ß-cyanoethyl, $\mathbf{R^{4B}}$ is o-/p-chlorophenyl and $\mathbf{R^1}$ is a linkage to a solid support.

22. A composition of claim 21, in which $\mathbf{R^1}$ is a tritylether linkage to Controlled-Pore-Glass (CPG).

23. A combinatorial set of compounds with core structure M and having a plurality of reactive moieties, containing blocking groups, wherein at least three groups are independently removable under different conditions, thereby allowing selective derivatization after deblocking and wherein one functional group is utilized for immobilization.

24. A combinatorial set of compounds according to claim 23 in which the reactive moieties are selected from the group consisting of OH, SH, NH_2, CO_2H, SOH, SO_2H SO_3H, CHO, keto, phosphate, phosphite, phosphoamidite, halogen, CN, CNS, NCS, NCO and derivatives thereof.

25. A combinatorial set of compounds according to claim 23 in which M is a multifunctional low molecular weight compound of general formula MD_n, wherein D represents the same or different independently deprotectable moieties and n an integer from 3 to 10.

26. A combinatorial set of compounds according to claim 23 selected from the group consisting of a: saccharide, aminosugar, deoxysugar, nucleoside, nucleotide, coenzyme, amino acid, lipid, steroid, vitamin, hormone, alkaloid and small molecule drug compound.

27. A combinatorial set of oligomeric compounds according to claim 23 selected from the group consisting of: an oligosaccharide, oligopeptide and oligonucleotide.

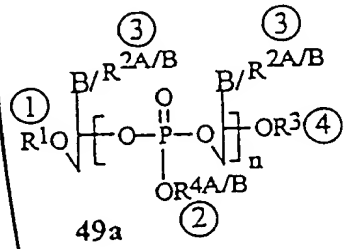
28. A combinatorial set of oligomeric compounds of claim 23 in which at one or more positions in the sequence a preselected set of building blocks is incorporated.

29. A combinatorial set of oligomeric compounds according to claim 28 in which different functional groups within each building block in the sequence can be addressed in a sequence specifically preprogrammed way and transformed with protecting or modification reagents in a regioselective form.

30. A combinatorial set of oligonucleotides according to claim 27 which are derived from 2'-deoxyribonucleosides or ribonucleosides.

31. A combinatorial set of oligonucleotides according to claim 30 consisting of natural and/or modified bases selected from the groups adenine, guanine, cytosine, uracil, 5-fluoro-uracil, 5-chloro-uracil, 5-bromo-uracil, 5-iodo-uracil, 5-fluoromethyl-uracil, 5-chloromethyl-uracil, 5-bromomethyl-uracil, 5-iodomethyl-uracil, 5-aminomethyl-uracil, 5-hydroxymethyl-uracil, 5-mercaptomethyl-uracil, 5-fluoro-cytosine, 5-chloro-cytosine, 5-bromo-cytosine, 5-iodo-cytosine, 5-azido-cytosine, 5-alkyl-cytosine, 5-ω-aminoalkyl-cytosine, 5-azido-uracil, 5-alkyl-uracil, 5-ω-aminoalkyl-uracil, 5-methyl-cytosine, 5-amino-cytosine, 5-amino-uracil, 4-triazolo-uracil, 4-triazolo-thymine, 4-tetrazolo-uracil, 4-tetrazolo-thymine, hypoxanthine, xanthine, 2,6-diamino-purine, 6-chloro-purine, 2,6-dichloropurine, 6-thio-purine, 2-thio-purine, 8-fluoro-adenine, 8-chloro-adenine, 8-bromo-adenine, 8-iodo-adenine, 8-fluoro-guanine, 8-chloro-guanine, 8-bromo-guanine, 8-iodo-guanine, 8-amino-adenine, 8-amino-guanine, 8-hydroxy-adenine, 8-hydroxy-guanine, 8-thio-adenine, 8-thio-guanine, N7-deaza-adenine, N7-deaza-guanine, N3-deaza-adenine, N3-deaza-guanine, N9-deaza-adenine, N9-deaza-guanine.

32. A combinatorial set of oligonucleotides according to claim 31 represented by the general formula **49a**:



49a

$B/R^{2A/B} = B$ or B^{R2A} or B^{R2B}

$R^{4A/B} = R^{4A}$ or R^{4B}

$R^{2A/B} = R^{2A}$ or R^{2B}

in which n is an integer from 1 to 100 and ①, ②, ③, ④ are positions in the molecule which can be addressed regioselectively and in which B represents a natural or modified nucleobase which does not need a protecting group during synthesis, B^{R2A}, B^{R2B} is a natural or modified nucleobase with a protecting group and R^{2A}, R^{4A}, R^{1} R^{3} represent different protecting groups that permit the creation of a combinatorial set of oligonucleotides with 16 possible states of protection or subsequent derivatization at ①- ④ and R^{2B}, R^{4B} represent protecting groups which are stable during deprotection and/ or subsequent derivatization at ①- ④.

33. A combinatorial set of oligonucleotides according to claim 32 in which R^{2A} or R^{2B} is a base protection group selected from the group of acyl groups such as acetyl, benzoyl, anisoyl, p-/o-tolyl, phenoxyacetyl, t-butylphenoxyacetyl or 2-nitrophenylsulfenyl (nps), 2-(4-nitrophenyl)-ethoxycarbonyl (npeoc), 2-(4-nitrophenyl)-ethyl (npe), 9-fluorenylmethoxycarbonyl (Fmoc), benzyloxycarbonyl, benzyl, allyloxycarbonyl, N,N-dimethylaminomethylidene (DMM) and derivatives thereof, p-nitrobenzylidene, levulinyl, compound **50** or derivatives thereof, compound **51**, trityl, monomethoxytrityl, dimethoxytrityl, trimethoxytrityl, 2,2,2-trichloro-*tert*-butyloxycarbonyl (TCBOC), R^{4A} or R^{4B} are phosphate protecting groups such as alkyl, aralkyl, allyl, ß-cyanoethyl, o-/-p-chlorophenyl, 2,5-dichlorophenyl, trichloroethyl, tribromoethyl, sulfonylethyl or derivatives thereof, 4-*tert*-butyl-2-chloro-phenyl, phenylmethylamino, 2,4-dichlorophenyl, m-chlorophenyl, o-fluorophenyl, benzyl, benzhydryl, ß,ß,ß-trichloroethyl, 4-nitro-2-chloromethyl-phenyl, 2-(4-nitrophenyl)-ethyl (npe), 4-nitrophenyl, compound 52 and 53, R^{3} is the 3'-OH functionality, which can be a

trityl, substituted trityl, triphenylmethoxyacetyl, diphenyl-*tert*-butylsilyl, succinyl, ß-benzoylpropionyl, levulinyl, *tert*-butyl-dimethyl-silyl, 2,4-dinitrophenylsulfenyl (dnps), 9-fluorenylmethoxycarbonyl (Fmoc), 3-{4-[bis-(4-methoxyphenyl)-methyl]-phenyl}-propionyl, 5-{3-[bis-(4-methoxyphenyl)-hydroxymethyl]-phenoxy}-levulinyl, 5-{3-[bis-(4-methoxyphenyl)-methoxymethyl]-phenoxy}-levulinyl or the linkage to a solid support and R^1 are 5'-OH functionalities selected from the same group as R^3.

34. A combinatorial set of oligonucleotides according to claim 32 in which R^{2A} are the 2-nitrophenylsulfenyl (nps) groups, for R^{2B} the 2-(4-nitrophenyl)-ethoxycarbonyl (npeoc) and 2-(4-nitrophenyl)-ethyl (npe) or npeoc groups, for R^3 the 5-{3-[bis-(4-methoxyphenyl)-hydroxymethyl]-phenoxy}-levulinyl or 5-{3-[bis-(4-methoxyphenyl)-methoxymethyl]-phenoxy}-levulinyl groups, for R^{4A} the ß-cyanoethyl groups, for R^{4B} the o-/p-chlorophenyl groups and R^1 is a linkage to a solid support.

35. A combinatorial set of oligonucleotides according to claim 32, in which R^1 is a tritylether linkage to Controlled-Pore-Glass (CPG).

36. A combinatorial set of oligonucleotides according to claim 32, which have been synthesized using the phosphoamidite, H-phosphonate or phosphotriester synthesis method.